particular, at the bottom half of page 7. No new matter has been added.

Entry of this Amendment is proper under 37 CFR § 1.116 because the Amendment: (a) places the application in condition for allowance; (b) does not raise new issues requiring further search and/or consideration; (c) satisfies the requirement of form asserted in the Final Rejections; (d) does not present additional claims without canceling a corresponding number of finally-rejected claims; and (e) places the application in better form for appeal, should an appeal be necessary.

II. Rejections Under 35 USC § 112, First Paragraph

At the outset, Applicants stress three points that relate to several of the following grounds of rejection: (1) claims 1-7, 9-14 and 20 are ***compound*** claims and, therefore, embody ***non-therapeutic*** utilities as well as therapeutic ones; (2) enablement must be evaluated taking into account the claim scope (MPEP §§ 2164.01 and 2164.08); and (3) imputing therapeutic limitations for the purpose of evaluating enablement, or any other purpose, is improper.

Claims 1-7 and 9-20 stand finally rejected under 35 USC § 112, first paragraph "for lack of enablement of how to use." Applicants respectfully traverse this rejection.

Applicants note that the standard for enablement is whether one of skill in the art would be able to practice the invention without resort to undue experimentation. MPEP § 2164.02. It is the burden of the Examiner to put forth a "reasonable basis to question the enablement provided for the claimed invention." MPEP § 2164.04. Hence, the Examiner has failed to substantiate a *prima facie* case demonstrating lack of enablement because there

is no evidence put forth that undue experimentation would be required to use the invention.

In the current Office Action, the Examiner provides three enumerated bases for this rejection. For the convenience of the Examiner, Applicants respond to these bases in numerical order below.

1. The first basis of rejection is that "the dosage problem remains." The Examiner contends, in essence, that the dosage information provided in the specification is confusing. Applicants submit, first, that specific dosage information is unnecessary to enable the instant invention and, second, that an allegedly unclear statement in the specification does not affect enablement.

First, the Examiner will recognize that clinical data are not required for enablement. See MPEP § 2107.02. As set forth below, the specification contains both *in vitro* and animal data relevant to dosage. The next step is human clinical trials. Thus, the Examiner improperly holds the instant invention to an enablement standard that can only be met with clinical data. This is true *a fortiori* for claims 1-7, 9-14 and 20, which are directed to ***compounds*** and, thus, do not rely on pharmaceutical applications for enablement. Hence, insofar as the rejection of claims 1-7, 9-14 and 20 relies on imputed therapeutic limitations, it is improper.

Furthermore, in view of the instant specification, the clinical data needed to determine suitable dosage requires only the kind and amount of routine experimentation endemic to any clinical trial. Indeed, determining a suitable, non-toxic dosage regimen is a primary purpose of clinical trials. Using standard dose escalation protocols, this determination is routinely made for ***every drug*** undergoing clinical investigation. Accordingly,

considering the vast number of drugs that have undergone clinical investigation, there is a ***very high level of skill*** in the art.

The Examiner will also note that the instant compounds are substituted xanthine derivatives and that the clinician would have experience with substituted xanthines. See, for example, GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 7th ed., pp. 589-603 (Macmillan Publishing Co., N.Y. 1985). Further, at least some embodied compounds are structurally similar to lisofylline, a drug that has been the subject of clinical investigation. Hence, considering the clinical experience with structurally similar compounds and the high level of skill in the art, it is reasonable to conclude that determining suitable dosage would not require undue experimentation. See TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH -- ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS.[1]

Second, this conclusion is unaltered with respect to alleged confusion in the specification. The specification offers general guidance to the clinical investigator. This investigator will recognize that the specification does not teach radical departures from established protocols and common sense. Accordingly, any perceived confusion in the specification would be overlooked, or at least viewed in light of conventional clinical wisdom. The artisan would not, therefore, be unable to practice the instant invention based on the belief that the drug

---

[1] "It is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. Section 112."

must be administered "1000 times a day." The level of skill in this art is sufficiently high that any such perception would immediately be dismissed.

Furthermore, the specification provides ample enabling guidance with respect to dosage. For example, the first full paragraph on page 9 discloses a suitable daily dose of "about 0.1 mg/kg to about 1000 mg/kg." The next paragraph discloses doses of "about 50 mg to about 5000 mg per day." Finally, Examples 22-24 provide guidance with respect to *in vitro* systems and Example 25 provides the treatment of dogs with representative compounds and provides further dosage guidance. In view of this guidance and the high level of skill in this well-developed art, one could use the invention with only the usual, routine experimentation inherent in the art. Accordingly, Applicants submit that this ground of rejection fails to establish a *prima facie* case and, therefore, request its withdrawal.

2. The Examiner next appears to assert the existence of allegedly non-operative embodiments as evidence of non-enablement. The Examiner contends "[t]he notion that these compounds are all prodrugs is simply not credible [because] [o]rdinary ethers cannot be significantly hydrolyzed by the body ...." Applicants submit that the Examiner is improperly reading a "prodrug" limitation into the claims.

The Examiner is reminded that claims 1-7, 9-14 and 20 are directed to ***compounds*** which, due to selective chemical structures, provide for selective control of the extent and rate of hydrolysis of these compounds to a hydroxyl-substituted xanthine compound. A need for such differing hydrolytic potential may arise in the context of a synthetic method, not exclusively in the context of a therapeutic application. The Examiner is also reminded that, although directed to

"pharmaceutical composition[s]," claims 15-19 do not contain a "prodrug" limitation either.

Furthermore, even if the claims were directed to "prodrugs," the existence of non-operative embodiments is insufficient to conclude that the invention is not enabled. The Examiner's attention is directed to the following passage from the USPTO enablement training materials:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)(prophetic examples do not make the disclosure non-enabling).

As a person skilled in the art, the Examiner has concluded that specific embodiments are inoperative. If the Examiner were correct, Applicants submit that other skilled artisans would be able to make the same determination without expending effort on any experimentation, undue or otherwise. Accordingly, Applicants request withdrawal of this ground of rejection.

3. The Examiner next avers that "applicants have not presented evidence that lisofylline has actually been shown useful for anything." Thus, the Examiner's reasoning appears to be as follows: (a) the instant compounds are prodrugs of lisofylline; (b) the sole usefulness of the inventive compounds is as lisofylline prodrugs; (c) lisofylline is not "useful for anything;" therefore (d) the present compounds are not "useful for anything."

Applicants reiterate that the instant claims are not directed to "prodrugs" of lisofylline or "prodrugs" of any other drug, rather they are directed to **compounds** with a variety of asserted utilities. Further, without admitting the soundness of this logic, Applicants submit that this rejection sounds in lack of utility, not lack of enablement. Thus, the test for enablement is not whether a compound is "useful for anything," rather, it is whether one skilled in the art would be able to use the inventive compounds without undue experimentation. The "useful for anything" standard asserted by the Examiner seems more appropriate to 35 USC § 101. Moreover, the Examiner cited 35 USC § 101 as authority for this *same rejection* in the Action dated September 21, 1995. Applicants, therefore, conclude that the Examiner is asserting that the instant compounds have no utility, which is improper under the current rejection.

Because the Examiner has failed to provide any evidence supporting the conclusion that the inventive compounds, or even lisofylline, are not "useful for anything," Applicants submit that this rejection is improper. Thus, it is not the Applicants' burden to "present[] evidence that lisofylline has actually been shown useful for anything." Rather, it is the Examiner's burden to provide particularized findings regarding the incredible nature of each asserted utility, such as those listed on pages 1 and 2 of the specification. MPEP § 2107.01(d). Because the Examiner has failed to meet this burden, Applicants respectfully request removal of this ground of rejection.

III. Rejections Under 35 USC § 112, First and Second Paragraphs

Claims 1-7 and 9-20 stand rejected under the first and second paragraphs of section 112 for twenty-one enumerated reasons. While applicants respectfully traverse all of these grounds of rejection, in the interest of advancing the prosecution of this application, they have amended some claims

and offer comments for further clarification. Again, for the convenience of the Examiner, Applicants address these reasons in numerical order.

1. Claims 1, 15 and 20 have been amended to recite "carbohydrate-moiety," thereby indicating the free-valence form of a carbohydrate.

2. Applicants note that the third-last and the last species of claim 14 are embodied in the formula $-OX(R_5)_m$. Thus, Applicants do not rely on the recitation of "naturally occurring amino acid" in support of this structure. Claim 1 has been amended to specifically recite R_5 as "dimethylamino" in accordance with next-last structure.

3. This point addresses Applicants' attempts to claim the compounds of Formula I as an ether moiety. Accordingly, claim 1 has been further amended. Specific support for this amendment is found in the specification on page 7, lines 27-30.

4. As discussed above, "pharmaceutical" is not a recitation of claims 1-7, 9-14 and 20. These claims are directed to ***compounds***. Moreover, with respect to claims 15-19, even assuming the Examiner has identified a non-operative embodiment, as detailed above, this is insufficient to substantiate a rejection for lack of enablement. Again, if the Examiner can identify non-operative embodiments as one of skill in the art, Applicants submit that so can others skilled in the art. Thus, no undue experimentation is required and these claims, therefore, are enabled.

5. Applicants submit that "substituted" is sufficiently clear to one of skill in the art, even without resort to the specification. The Examiner's attention, however, is directed

to the specification at page 7, line 21-27 for examples of permissible substituents.

6. Applicants submit that "prodrug of lisofylline" is not a limitation of any of the present claims. Further, as set forth above, the instant compounds have utility outside any reliance on functioning as a prodrug of lisofylline or any other medicament. Accordingly, a chain-length that would prevent a given compound from functioning as a lisofylline prodrug is not relevant to enablement of these claims.

7. Claim 6 has been amended merely to reflect more conventional nomenclature.

8. While Applicants submit that this recitation is clear, claims 1, 15 and 20 have been amended to indicate that the ester linkage is through an oxygen atom.

9. Claims 1, 15 and 20 have been amended to more particularly point out the nature of the "heterocyclic group." Thus, the "nature and number of the heteroatoms" is recited. With regard to the nature of permitted substitutents, the Examiner's attention is directed to page 7, the paragraph beginning at line 19.

10. Applicants submit that "acetoxyalkyl" is appropriate to describe moieties such as that in compound 4547R, found in the specification at page 9, line 20. Thus, this term is clear and it finds support in the specification.

11. Species 10 of claim 14 has been deleted.

12. The recitation of "alkyl" has been removed from the terms at issue in claim 6 in order to reflect more conventional nomenclature.

13. Although Applicants submit that this recitation is clear, the recitation of "primary, secondary or tertiary" has been deleted from claim 6. It is noted that this amendment in no way alters the scope of this claim.

14. The terms to which the Examiner points have been deleted from claim 6.

15. Claim 10 has been amended to clarify the nature of these substituents.

16. The term "moiety" has been added to the substituent at issue to indicate its free-valence form.

17. The term "cyclopropyl" has been deleted.

18. The terms at issue have been amended in accord with more conventional nomenclature.

19. The terms "sulfonyl" and "sulfoxyl" have been deleted.

20. Applicants submit that "carbocycle" is sufficiently clear and definite. Furthermore, it is irrelevant whether the "point of attachment" is the carbocycle itself or a substituent. The Examiner contends, in essence, that the claim is indefinite because it does not recite whether the point of attachment is the carbocyclic ring or a substituent. Thus, the Examiner recognizes the definite possibilities. As set forth above, the artisan would readily understand the nature of possible substituents and, therefore, is apprised of the full meaning of this recitation. For examples of ring attachment and substituent attachment, the Examiner's attention is directed to claim 14, species 6 and 15. Accordingly, Applicants submit that this recitation is not indefinite.

21. Claim 9 has been amended in the interest of conforming to claim 1.

Because all twenty-one grounds for these rejections have been obviated by the above-detailed amendments and comments, Applicants respectfully request that the Examiner reconsider these rejections and withdraw them.

IV. Prior Art Rejections

The Examiner maintains prior art rejections over EP 286041 ("EP '041") and WO 93/17684 ("WO '684). These rejections rely on the alleged disclosure of a compound with a methoxy group at the R_4 position by EP '041 and a compound with a trifluorophenylacetic acid ester group at the R_4 position in WO '684. Applicants respectfully traverse these rejections. However, in the interest of advancing prosecution, the claims have been amended as set forth below.

First, claims 1-4, 6-8 and 10 are rejected under 35 USC § 102(b) as anticipated by EP '041. Applicants note the proviso in amended claim 1 which obviates this rejection.

Second, claims 1-7, 10, 11, 15-17 and 19 are rejected under 35 USC § 102(b) as anticipated by WO '684. Applicants note that amended claims 1 and 15 recite specific substituents of an R_5 carbocyclic moiety and that this recitation clearly does not embody the compound cited by the Examiner.

Third, claim 20 is rejected under 35 USC § 103 as obvious over EP '041 or WO '684 as being drawn to chain homologs of the above compounds. Applicants note that amended claim 20 reflects the same changes as claims 1 and 15 and, thus, clearly does not embody the disclosed compounds or obvious variants thereof.

Because all three prior art rejections are based on the disclosure of the aforementioned compounds and the amended claims do not embody these compounds or their obvious variants, Applicants submit that these rejections are all overcome. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw all three rejections.

V. Conclusions

In view of the foregoing, Applicants submit that the present claims are in condition for allowance. Should the Examiner have any questions regarding the present application or believe that further discussion will advance prosecution, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,

April 18, 1997
Date

Reg No. 40,244
for Stephen A. Bent
Reg. No. 29,768

FOLEY & LARDNER
Suite 500
3000 K Street, N.W.
Washington, DC 20007-5109
(202) 672-5300